

AMENDMENT TO THE CLAIMS

The present document amends claims 4-6, 24, 55, 56, 59, 60, 65 and 68-82, and adds claims 84-88. According to 37 C.F.R. § 1.121(c), after entry of the present amendment, the status of the claims in the case is as follows:

Claims 1-3 canceled

4. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine, ~~H₂O₂ or thrombin~~, or
- (d) a compound that interferes with tubulin activity; ~~or~~
- (e) ~~a calcium flux inducing agent.~~

5. (Currently Amended) The method of claim 4, wherein said at least a first antibody, or antigen-binding fragment thereof, binds to a phosphatidylethanolamine-protein complex on the luminal surface of blood vessels of the vascularized tumor.

6. (Currently Amended) The method of claim 4, wherein said at least a first antibody, or antigen-binding fragment thereof, binds to a phosphatidylserine-protein complex on the luminal surface of blood vessels of the vascularized tumor.

7. (Previously Presented) The method of claim 4, wherein said at least a first antibody is an IgG or IgM anti-aminophospholipid antibody.

8. (Previously Presented) The method of claim 4, wherein said at least a first antigen-binding fragment of an antibody is an scFv, Fv, Fab', Fab or F(ab')₂ antigen-binding fragment of an anti-aminophospholipid antibody.

9. (Previously Presented) The method of claim 4, wherein said at least a first antibody is a human, humanized or part-human chimeric anti-aminophospholipid antibody or antigen-binding fragment thereof.

Claim 10 canceled

Claims 11-22 canceled

23. (Previously Presented) The method of claim 4, wherein said at least a first antibody is a dimer, trimer or multimer of an anti-aminophospholipid antibody or antigen-binding fragments thereof.

24. (Currently Amended) The method of claim 4, wherein at least a second antibody that binds to an aminophospholipid-protein complex, or an antigen-binding fragment thereof, is administered to said animal.

25. (Previously Presented) The method of claim 4, wherein said at least a first pharmaceutical composition is administered to said animal via intravenous administration.

26. (Original) The method of claim 4, wherein an image of the vasculature of said vascularized tumor is first obtained by administering to said animal a diagnostically effective amount of a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to and identifies an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor.

27. (Original) The method of claim 4, further comprising subjecting said animal to surgery or radiotherapy.

Claims 28-40 canceled

41. (Original) The method of claim 4, wherein said animal is a human patient.

Claims 42-48 canceled

49. (Previously Presented) The method of claim 4, wherein said at least a second therapeutic agent is a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B.

50. (Previously Presented) The method of claim 49, wherein said at least a second therapeutic agent is carmustine, cytosine arabinoside, methotrexate, aminopterin, demecolcine, mithramycin, chlorambucil, melphalan, daunorubicin, doxorubicin, verapamil, tamoxifen, taxol, vincristine, vinblastine, etoposide, 5-fluorouracil (5FU), camptothecin, actinomycin-D, mitomycin C, cisplatin, a combretastatin or cyclophosphamide.

51. (Previously Presented) The method of claim 4, wherein said at least a second therapeutic agent is an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C.

52. (Previously Presented) The method of claim 51, wherein said at least a second therapeutic agent is angiostatin or endostatin.

53. (Previously Presented) The method of claim 4, wherein said at least a second therapeutic agent is an inflammatory cytokine.

54. (Previously Presented) The method of claim 53, wherein said at least a second therapeutic agent is interleukin-4.

55. (Currently Amended) The method of claim ~~[[4]]~~ 73, wherein said at least a second therapeutic agent is H₂O₂.

56. (Currently Amended) The method of claim ~~[[4]]~~ 73, wherein said at least a second therapeutic agent is thrombin.

57. (Previously Presented) The method of claim 4, wherein said at least a second therapeutic agent is a compound that interferes with tubulin activity.

58. (Previously Presented) The method of claim 57, wherein said at least a second therapeutic agent is taxol, vincristine, vinblastine, bleomycin, or a combretastatin.

59. (Currently Amended) The method of claim ~~[[4]]~~ 73, wherein said at least a second therapeutic agent is a calcium-flux inducing agent.

60. (Currently Amended) The method of claim ~~[[4]]~~ 59, wherein said at least a second therapeutic agent is a calcium ionophore.

61. (Previously Presented) The method of claim 4, wherein said at least a first antibody and said at least a second therapeutic agent are administered to said animal simultaneously.

62. (Previously Presented) The method of claim 4, wherein said at least a first antibody and said at least a second therapeutic agent are administered to said animal sequentially.

63. (Previously Presented) The method of claim 62, wherein said at least a second therapeutic agent is administered to said animal prior to said at least a first antibody.

64. (Previously Presented) The method of claim 63, wherein said at least a second therapeutic agent injures or induces apoptosis in the endothelium of the blood vessels of said vascularized tumor.

65. (Currently Amended) The method of claim 64, wherein said at least a second therapeutic agent is taxol, vincristine, vinblastine, neomycin, a combretastatin, a podophyllotoxin, TNF- α , angiostatin, endostatin, vasculostatin, an $\alpha_v\beta_3$ antagonist, ~~a calcium ionophore or a calcium flux inducing agent~~; or is a prodrug thereof.

66. (Previously Presented) The method of claim 62, wherein said at least a second therapeutic agent is administered to said animal subsequent to said at least a first antibody.

67. (Previously Presented) The method of claim 66, wherein said at least a second therapeutic agent is an anti-tumor cell immunotoxin or an anti-angiogenic agent.

68. (Currently Amended) A method for treating cancer, comprising simultaneously or sequentially administering to an animal having a vascularized tumor a therapeutically effective

combination of ~~an~~ at least a first pharmaceutical composition comprising at least a first unconjugated antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid a phosphatidylserine-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine; or
- (d) a compound that interferes with tubulin activity.

69. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first unconjugated antibody, or antigen-binding fragment thereof, that targets and binds to phosphatidylethanolamine on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine, H_2O_2 or thrombin; or

- (d) a compound that interferes with tubulin activity;~~or~~
- (e) ~~a calcium flux inducing agent.~~

70. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first scFv, Fv, Fab', Fab or F(ab')₂ antigen-binding fragment of an antibody that targets and binds to an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine, ~~H₂O₂ or thrombin;~~ or
- (d) a compound that interferes with tubulin activity;~~or~~
- (e) ~~a calcium flux inducing agent.~~

71. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first human, humanized or part-human chimeric antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid-protein complex on the luminal surface of blood

vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine, H_2O_2 or thrombin; or
- (d) a compound that interferes with tubulin activity; or
- (e) ~~a calcium flux inducing agent.~~

72. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a ~~therapeutically effective combination~~ tumor-destructive amount of at least a first pharmaceutical composition comprising at least a first ~~dimer, trimer or multimer of an~~ antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine, H_2O_2 or thrombin; or
- (d) a compound that interferes with tubulin activity; or

- (e) ~~a calcium flux inducing agent.~~

73. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising administering to said animal ~~via intravenous administration~~ a therapeutically effective amount of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and simultaneously or sequentially administering to said animal a therapeutically effective amount of at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine, H₂O₂ or thrombin;
- (d) a compound that interferes with tubulin activity; or
- (e) a calcium flux inducing agent.

74. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising:

- (a) forming an image of the vasculature of said vascularized tumor by administering to said animal a diagnostically effective amount of a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to and identifies an

aminophospholipid on the luminal surface of blood vessels of the vascularized tumor; and

- (b) simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:
 - (i) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
 - (ii) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
 - (iii) an inflammatory cytokine, ~~H₂O₂ or thrombin~~; or
 - (iv) a compound that interferes with tubulin activity; ~~or~~
 - (v) ~~a calcium flux inducing agent.~~

75. (Currently Amended) A method for treating a human patient having a vascularized tumor, comprising simultaneously or sequentially administering to said patient a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine, H_2O_2 or thrombin; or
- (d) a compound that interferes with tubulin activity; ~~or~~
- (e) ~~a calcium flux inducing agent.~~

76. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is a compound that interferes with tubulin activity.

77. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is taxol, vincristine, vinblastine, bleomycin or a combretastatin.

78. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a ~~therapeutically effective combination~~ tumor necrosis-inducing amount of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine, ~~H₂O₂ or thrombin~~; or
- (d) a compound that interferes with tubulin activity; ~~or~~
- (e) ~~a calcium flux inducing agent.~~

79. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a ~~therapeutically effective combination~~ of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid-protein complex on the luminal surface of tumor blood vessels of the vascularized tumor in an amount effective to destroy or occlude at least a portion of said tumor blood vessels; and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine, H_2O_2 or thrombin; or
- (d) a compound that interferes with tubulin activity; ~~or~~
- (e) ~~a calcium flux inducing agent.~~

80. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent injures or induces apoptosis in the endothelium of the blood vessels of said vascularized tumor.

81. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first antibody, or antigen-binding fragment thereof, that targets and binds to an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is taxol, vincristine, vinblastine,

neomycin, a combretastatin, a podophyllotoxin, TNF- α , angiostatin, endostatin, vasculostatin, an $\alpha_v\beta_3$ antagonist, ~~a calcium ionophore or a calcium flux inducing agent~~; or is a prodrug thereof.

82. (Currently Amended) A method for treating an animal having a vascularized tumor, comprising simultaneously or sequentially administering to said animal a therapeutically effective combination of at least a first pharmaceutical composition comprising at least a first unconjugated antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent; wherein said second therapeutic agent is:

- (a) a chemotherapeutic agent selected from the chemotherapeutic agents listed in Table B;
- (b) an anti-angiogenic agent selected from the anti-angiogenic agents listed in Table C;
- (c) an inflammatory cytokine, ~~H₂O₂ or thrombin~~; or
- (d) a compound that interferes with tubulin activity; ~~or~~
- (~~e~~) ~~a calcium flux inducing agent.~~

83. (Previously Presented) The method of claim 4, wherein said at least a first antibody is an anti-aminophospholipid monoclonal antibody or antigen-binding fragment thereof.

84. (New) The method of claim 4, wherein said at least a first antibody, or antigen-binding fragment thereof, binds to a phosphatidylserine and β_2 -glycoprotein I complex on the luminal surface of blood vessels of the vascularized tumor.

85. (New) The method of claim 73, wherein said at least a second therapeutic agent is administered to said animal via direct instillation into said vascularized tumor.

86. (New) The method of claim 82, wherein said at least a first antibody, or antigen-binding fragment thereof, binds to phosphatidylethanolamine on the luminal surface of blood vessels of the vascularized tumor.

87. (New) The method of claim 82, wherein said at least a first antibody, or antigen-binding fragment thereof, binds to phosphatidylserine on the luminal surface of blood vessels of the vascularized tumor.

88. (New) The method of claim 82, wherein said at least a first antibody, or antigen-binding fragment thereof, binds to an aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor.